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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/582,680

04/16/2007

Jo Klaveness

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06/24/2009

GE HEALTHCARE, INC.

IP DEPARTMENT 101 CARNEGIE CENTER

PRINCETON, NJ 08540-6231

EXAMINER

SCHLIENTZ, LEAH H

ART UNIT

PAPER NUMBER

1618

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/582,680	Applicant(s) KLAVENESS ET AL.	
	Examiner Leah Schlientz	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4,6-8 and 11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4,6-8 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/14/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 4/9//2009, in reply to the Office Action mailed 12/9/2009, is acknowledged and has been entered. Claims 1-4, 6-8 and 11 have been amended. Claims 5, 9, 10, 12 and 13 have been cancelled. Claims 1-4, 6-8 and 11 are pending and are examined herein on the merits for patentability.

Information Disclosure Statement

Copies of the foreign references cited in the information disclosure statement (IDS) submitted on 6/14/2006 were received with the Response filed 4/9/2009, and have been considered by the examiner. A copy of the signed IDS is provided herewith.

Response to Arguments

Applicant's arguments have been considered but are moot in view of new ground(s) of rejection. Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of optical imaging of vulnerable atherosclerotic plaque of an animate subject involving administering an optical contrast agent with an affinity for an abnormally expressed biological target associated with vulnerable atherosclerotic plaques, wherein said biological target is selected from: MMP 9, toll-like receptors, scavenger receptors, oxidized LDL, oxidation products of lipids and their adducts with proteins, angiotensin II receptors and collagens. Dependent claims define that the contrast agent has the formula V-L-R, wherein V is one or more vector moieties having affinity for an abnormally expressed target in vulnerable atherosclerotic plaques, L is a linker moiety or a bond and R is one or more reporter moieties detectable in vivo optical imaging. However, the claims are devoid of any structural elements that correlate to the function which is to be achieved with the claimed composition. For example, a vast number of potential "vector moieties having an affinity for an abnormally expressed target in vulnerable atherosclerotic plaques" may be found in the art to be capable of having the claimed function. Applicant has identified in the instant specification a diverse variety of targets for which the vector may have affinity including MMP 9, toll-like receptors, scavenger receptors, oxidized LDL, oxidation products of lipids and their adducts with proteins, angiotensin II receptors and collagens, etc. (see

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paragraphs 0025-0044 of the instant specification). Such targets are widely varying in structure and would have an almost unlimited number of potential vectors which may have affinity thereto. The vectors themselves may be almost unlimited including various peptide sequences, small molecules, antibodies, nucleic acid sequences, etc. It is clear that Applicant had possession of such a few specific formulations at the time of filing using specific and defined vectors as identified in paragraphs 0057-0067 and 0088-0095 and the Examples, but the specification as originally filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed contrast agent, one would have to determine the type of vector having affinity to which out of an extremely large number of targets to conjugate to which out of an almost unlimited number of potential optical imaging moieties to be combined into a single agent, and further which out of an almost unlimited number of potential functional groups or chemical reactions would be necessary to derivatize and conjugate the moieties into a single agent having the claimed functional properties, in order to provide a contrast agent to practice the claimed method. One would have to select which portions of which molecules would be suitable to be conjugated to the others and on what positions of the molecules with various substituents. Applicant's limited disclosure of a particular compound which has the claimed functional properties for use in the claimed method does not provide support that Applicant envisaged the invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an

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indication of what the agent does, rather than what it is. See MPEP 2163 and *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406.

Applicant argues on pages 5-6 of the Response that the amended claims are now limited to a method of optical imaging of vulnerable atherosclerotic plaque of an animate subject and that the claims are no longer to optical imaging contrast agents *per se*. Hence, it can no longer be argued that the claim pertains to compounds defined only by their function. Applicant further argues that in addition, the claim scope has been limited to the preferred biological targets described in the specification at page 8 lines 1 to 5. Applicant further argues that the specification provides sufficient information for the person skilled in the art to reproduce the method of amended claim 1, such that the specification provides suitable optical reporters; a description of suitable optical imaging techniques, a description of targeting molecules and methods of labelling them with optical reporters. The person skilled in the art can either use the contrast agents described in the specification, or generate new ones. Applicants suggest that the claim scope for such an optical imaging method claim should not be limited by the possible future advent of new targeting molecules. If a person skilled in the art has available a compound with affinity for one of the targets described, then labelling such a compound with an optical reporter is taught by the present specification.

This is not found to be persuasive. In order to practice the claimed method, one would necessarily be in possession of the contrast agent, thus a reasonable description of the contrast agent which are used to practice the method is necessary. While Applicant has provided a description of a few specific vectors (i.e. a single peptide

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sequence which binds MMP (paragraph 0088), a single hydrazine derivative which targets oxidation product of phospholipid (0095) and a single small molecule which acts as a vector for angiotensin (paragraph 0067). Such a limited disclosure of a single vector for each of the claimed receptors which are associated with atherosclerotic plaque (MMP 9, toll-like receptors, scavenger receptors, oxidized LDL, oxidation products of lipids and their adducts with proteins, angiotensin II receptors and collagens) does not provide sufficient description to show that Applicant was in possession of the full scope of a contrast agent comprising an optical imaging moiety and any vectors (e.g. any small molecule, any peptide, any oligonucleotide, any antibody etc) which may target the claimed receptors. With regard to Applicant's argument that the claim scope should not be limited by the possible future advent of new targeting molecules, and that if a person skilled in the art has available a compound with affinity for one of the targets described, then labeling such a compound with an optical reporter is taught by the specification, this is not found to be persuasive because the specification has not provided a clear description of the full scope of targeting vectors which were envisaged at the time the specification was filed. Future-developed targeting moieties would not be encompassed by vectors that Applicant was in possession of at the time the application was filed, especially since Applicant has only described a single vector for each target/receptor.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6-8 and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Smith *et al.* (US 2004/0053823).

Smith discloses isolated MMP-2, MMP-9 and MT1-MMP selective substrate polypeptides or functional peptidomimetics. The selective substrate polypeptides contain the following sequences: MMP-9 selective substrate polypeptides contain SEQ ID NOS:28-35 (abstract). A diagnostic moiety can be linked to a selective substrate polypeptide of the invention in an inactive form. This type of diagnostic moiety would be targeted to a site of metalloproteinase activity where it would be activated. For example, a fluorescent probe such as a near-infrared fluorescence(NIRF) imaging probe can be in an inactive or quenched state until it reaches a desired site where it can be converted to an active or un-quenched state (paragraph 0079). A diagnostic moiety can also be, for example, a MRI contrast dye or a fluorescent agent. In one embodiment, the invention provides an isolated MT1-MMP, MMP-2, or MMP-9 selective substrate polypeptide of the invention described above where the diagnostic moiety is a quenched fluorophore, for example, a near-infrared fluorescence (NIRF)

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imaging probe. These biocompatible, optically quenched NIRF imaging probes can generate a strong NIRF signal after enzyme activation such as hydrolysis by a proteinase. A NIRF imaging probe can be linked to a MT1-MMP, MMP-2, or MMP-9 selective substrate polypeptide of the invention in order to specifically target the NIRF imaging probe to a site of activity of these MMPs such as a tumor or a site of inflammation. The NIRF moiety linked to a selective substrate polypeptide of the invention can be used to define and measure a site of MMP activity, for example, this conjugate can be used to image a tumor (paragraph 0088). See also claim 25, drawn to an MMP-9 selective substrate peptide sequence of SEQ ID 28-35 conjugated to a fluorophore diagnostic agent. The methods of the invention also can be useful for preferentially directing a moiety to angiogenic vasculature that is not tumor vasculature or associated with neoplastic disease. Neovascularization also has been described within the intima of human atherosclerotic lesions and, further, angiogenic inhibitors such as endostatin can reduce the intimal neovascularization and plaque growth evident in apolipoprotein E-deficient mice. Thus, a method of the invention can be useful for preferentially directing a therapeutic moiety or imaging agent to angiogenic sites in atherosclerotic plaques (paragraph 0127).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (US 2003/0170173), as evidenced by Penate *et al.* (*Cancer Research*, 2001, 61, p. 3978-3985).

Klaveness discloses contrast agents and the use of these contrast agents for diagnosis of diseases in humans and animals based on mapping of metabolic activity. The contrast agents can be used to identify tissue or cells with metabolic activity or enzymatic activity deviating from the normal (abstract). Contrast agents can be for optical imaging, including those having fluorophores, etc. (paragraph 0009 and 0107-0109). The contrast agents are conjugated with various enzymes substrates including MMP. Klaveness teaches that substrates For Human Matrix Metalloproteinase include Collagens, Proteoglycans, Laminin, Fibronectin, Gelatins, Elastin, Perlacan, Entactin, Vitronectin, Tenascin, Nidogen, Dermatan sulphate, proTNF-.A-inverted., Vitronectin, Aggrecan, Transin, Decorin, Glycoproteins. MMP could also be used according to the invention as possible targets for vulnerable atherosclerotic plaques. Reliable methods for targeting vulnerable atherosclerotic plaques are currently missing. Vulnerable

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plaques tend to rupture and induce thrombosis, which may lead to occlusion of the vessel and acute myocardial infarction. As a further aspect of the invention it is suggested to detect MMP activity as targets for distinguishing between stable and unstable vulnerable atherosclerotic plaques. Degradation of the fibrous cap in the atherosclerotic plaque by MMPs destabilises the plaque and increases its vulnerability. The activity of these MMPs, or the new epitopes exposed after metalloproteinases digestion, could be targets for contrast agents (paragraphs 0194-0197). See especially Example 25, drawn to a gelatinase-binding peptide for imaging atherosclerotic plaques, and contrast agents for imaging atherosclerotic plaques by MRI and scintigraphy. Gelatinase is a metalloproteinase that is expressed by unstable atherosclerotic plaques. The cyclic peptide Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys was identified as a gelatinase inhibitor and is synthesized by solid phase techniques. The peptide is conjugated to DTPA and complexed with gadolinium or ^{99m}Tc for use in MRI or scintigraphic imaging of atherosclerotic plaque. The contrast agents for detecting enzyme activity are characterized in that the contrast agent substrate changes pharmacodynamic properties and/or pharmacokinetic properties upon a chemical modification of the contrast agent substrate to a contrast agent product upon a specific enzymatic transformation (claim 4).

The Penate reference is included to show that the Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys peptide (CTT), is a gelatinase targeting peptide which inhibits MMP-2 and MMP-9 (see page 3978).

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Klaveness does not specifically conjugate Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys to an optical imaging contrast agent. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute an optical imaging agent such as a fluorescent dye for the DTPA chelates in Example 25 of Klaveness, and therefore to use such a contrast agent for optical imaging of vulnerable atherosclerotic plaque. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Klaveness teaches that a variety of contrast agent substrates may be used including MRI contrast agent, a radiopharmaceutical contrast agent, an ultrasound contrast agent, an optical imaging contrast agent or an x-ray contrast agent (claim 8). See also paragraphs 0009 and 0107-0190. Even though Klaveness does not specifically recite that Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys targets MMP-9, it is known in the art to inherently do so, as shown by Penate.

With regard to the Klaveness document, it is noted that Applicant argues on pages 9-10 of the Response that Klaveness teaches towards collagen as a possible labelled entity for imaging MMP activity in atherosclerotic plaque. Applicant asserts that the subject matter of present claim 1 is different, in that the claimed contrast agent has affinity for collagen. Thus, the contrast agent binds to collagen, because collagen is an "abnormally expressed biological target associated with vulnerable atherosclerotic plaque". The contrast agent does not comprise collagen itself, as taught by Klaveness. The teaching in this regard is thus clearly different from that of Klaveness, and that

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Klaveness in fact teaches away from present claim 1 by teaching towards collagen itself as a suitable imaging agent.

This is not found to be persuasive. The claims are not limited to collagen as an abnormally expressed biological target, e.g. MMP-9 and other targets are claimed, and Klaveness specifically teaches a vector directed to gelatinase targeting for atherosclerotic plaque imaging, Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys, known in the art to be an MMP-9 inhibitor.

Double Patenting

Claims 1-4, 6-8 and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/573,604, 10/573,606, 10/582,679, 10/582,842, and 10/582,893, for reasons set forth in the previous Office Action.

Applicant indicates on page 10 of the Response that a terminal disclaimer will be filed once the instant application is indicated as allowable. However, since no terminal disclaimer has been filed at this time, the claims stand rejected.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP §

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706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS